IN THE SPECIFICATION

On page 8, please amend the paragraph beginning on line 23 as follows:

In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) microinjecting or transfecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein said substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or, alternatively, the substrate is labeled with at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; (b) contacting the cell with a member of a library of compounds; and (c) measuring the activity of the tRNA splicing endonuclease wherein an antiproliferative compound that inhibits or reduces tRNA splicing endonuclease activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety in the presence of the compound is ~~decreaseed~~ increased relative to the absence of the compound or the presence of a negative control. In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting an animalia cell containing substrate of a tRNA splicing endonuclease with a member of a library of compounds, wherein the substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or, alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing endonuclease activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of a fluorescent donor moiety in the presence of the compound is ~~decreased~~ increased relative to the absence of the compound or the presence of a negative control.

On page 10, please amend the paragraph beginning on line 10 as follows:

In one embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting an animalia cell-free extract (preferably, a tRNA splicing endonuclease extract) or a purified animalia tRNA splicing endonuclease with a substrate of a tRNA splicing endonuclease and a member of a library of compounds,

wherein the substrate is labeled at the 5' end with a fluorophore and at the 3' end with a quencher, or, alternatively, the substrate is labeled at the 5' end with a quencher and labeled at the 3' end with a fluorophore; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing endonuclease activity is identified if a ~~greater~~ reduced fluorescent signal is detectable in the presence of the compound relative to the absence of the compound or the presence of a negative control. In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting an animalia cell-free extract (preferably, a tRNA splicing endonuclease extract) or a purified animalia tRNA splicing endonuclease with a substrate of a tRNA splicing endonuclease and a member of a library of compounds, wherein said substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or, alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing endonuclease activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety in the presence of the compound is increased relative to the absence of the compound or the presence of a negative control.

On page 25, please amend the paragraph beginning on line 21 as follows:

FRET assays can be utilized to identify a compound that modulates the activity of an animalia tRNA splicing endonuclease. The FRET cell-based assays described herein may be conducted by microinjecting or transfecting (*e.g.*, using liposomes or electroporation) a substrate for an animalia tRNA splicing endonuclease into a cell and contacting the cell with a compound, wherein the substrate is labeled at the 5' end with a fluorophore and labeled at the 3' end with a quencher, or, alternatively, the substrate is labeled at the 5' end with a quencher and labeled at the 3' end with a fluorophore, and measuring the fluorescence of the substrate by, *e.g.*, fluorescence microscopy or a fluorescence emission detector such as a Viewlux or Analyst. The endogenous tRNA splicing endonuclease will cleave the substrate and result in the production of a detectable fluorescent signal. A compound that inhibits or reduces the activity of the endogenous tRNA splicing endonuclease will prevent the production of a detectable fluorescent signal. Alternatively, the FRET cell-based assays may be conducted by microinjecting or transfecting a substrate for an animalia tRNA splicing

endonuclease into a cell and contacting the cell with a compound, wherein the substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or, alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety, and measuring the fluorescence of the substrate by, *e.g.*, fluorescence microscopy or a fluorescence emission detector such as a Viewlux or Analyst. The endogenous tRNA splicing endonuclease will cleave the substrate and result in the production of a detectable fluorescent signal by the fluorescent donor moiety and fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety. However, a compound that inhibits the activity of the endogenous tRNA splicing endonuclease will ~~reduce~~ increase the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety.

On page 63, please amend the paragraph beginning on line 6 as follows:

In a specific embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) microinjecting or transfecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein the substrate is labeled at the 5' end with a fluorophore and labeled at the 3' end with a quencher, or alternatively, the substrate is labeled at the 5' end with a ~~quenechr~~ quencher and labeled at the 3' end with a fluorophore; (b) contacting the cell with a member of a library of compounds; and (c) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing activity is identified if a fluorescent signal is not detectable in the presence of the compound relative to the absence of the compound or the presence of a control. In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting a animalia cell containing a substrate of a tRNA splicing endonuclease with a member of a library of compounds, wherein the substrate is labeled at the 5' end with a fluorophore and at the 3' end with a quencher, or alternatively, the substrate is labeled at the 5' end with a ~~quenchr~~ quencher and labeled at the 3' end with a fluorophore; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing activity is identified if a fluorescent signal is not detectable in the presence of the compound relative to the absence of the compound or the presence of a control.

On page 63, please amend the paragraph beginning on line 25 as follows:

In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) microinjecting or transfecting a substrate of a tRNA splicing endonuclease into a animalia cell, wherein the substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; (b) contacting the cell with a member of a library of compounds; and (c) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing activity is identified if the fluorescent signal detected in the presence of the compound is altered relative to the absence of the compound or the presence of a control. In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting a animalia cell containing a substrate of a tRNA splicing endonuclease with a member of a library of compounds, wherein the substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits or reduces tRNA splicing <u>endonuclease</u> activity is identified if a fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety in the presence of the compound is ~~reducred~~ <u>increased</u> relative to the absence of the compound or the presence of a control.

On page 66, please amend the paragraph beginning on line 24 as follows:

In one embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting an animalia cell-free extract (preferably, a tRNA splicing endonuclease extract) or a purified animalia tRNA splicing endonuclease with a substrate of a tRNA splicing endonuclease and a member of a library of compounds, wherein the substrate is labeled at the 5' end with a fluorophore and labeled at the 3' end with a quencher, or alternatively, the substrate is labeled at the 5' end with quencher and labeled at the 3' end with a fluorophore; (b) measuring the activity of the tRNA splicing endonuclease,

wherein an antiproliferative compound that inhibits or reduces tRNA splicing activity is identified if a fluorescent signal is not detectable in the presence of the compound relative to the absence of the compound or the presence of a control. In another embodiment, the invention provides a method of identifying an antiproliferative compound that inhibits or reduces animalia tRNA splicing endonuclease activity, said method comprising: (a) contacting an animalia cell-free extract (preferably, a tRNA splicing endonuclease extract) or a purified animalia tRNA splicing endonuclease with a substrate of a tRNA splicing endonuclease and a member of a library of compounds, wherein the substrate is labeled at the 5' end with a fluorescent donor moiety and labeled at the 3' end with a fluorescent acceptor moiety, or alternatively, the substrate is labeled at the 5' end with a fluorescent acceptor moiety and labeled at the 3' end with a fluorescent donor moiety; and (b) measuring the activity of the tRNA splicing endonuclease, wherein an antiproliferative compound that inhibits tRNA splicing activity is identified if the fluorescence emission of the fluorescent acceptor moiety at the wavelength of the fluorescent donor moiety detected in the presence of the compound is ~~decreased~~ increased relative absence of the absence of the compound or presence of a control.